DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Hugh L. Moore
Keith D. Parr
Terrence P. Canade
Deanne M. Mazzochi
Lord, Bissell & Brook
115 South LaSalle Street
Chicago, Illinois 60603

Re: Docket No. 00P-0499/CP1

Dear Mr. Moore, Mr. Parr, Mr. Canade, and Ms. Mazzochi:

This responds to your citizen petition, on behalf of Apotex, Inc., the TorPharm Division of Apotex, Inc. and Apotex Corporation (Apotex), dated February 3, 2000, and your comment, dated July 28, 2000, requesting that the Food and Drug Administration (FDA) do the following:

1. Remove two patents, U.S. Patent Nos. 5,872,132 ('132) and 5,900,423 ('423), from *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book),

2. Refuse to permit those or future patents claiming SmithKline Beecham Pharmaceuticals' (SmithKline's) paroxetine hydrochloride (Paxil) to interfere with or delay our review and approval of the abbreviated new drug application (ANDA) filed by Apotex for that drug product, and

3. Determine that the patent declarations submitted by SmithKline are deficient and do not support the patent listings.

As discussed below, the patents were properly listed in the Orange Book. Therefore, we deny the requests in your citizen petition and comment.

I. Background

FDA approved Paxil in 1992. SmithKline included information on U.S. Patent 4,721,723 ('723) in its new drug application (NDA 20-031), and patent '723 was listed in the Orange Book upon approval of the NDA. Apotex submitted an ANDA referencing Paxil on March 31, 1998, and filed a paragraph IV certification[1] claiming that its product would not infringe patent '723 and that patent '723 was invalid and unenforceable.

[1] See section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act.

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SmithKline sued Apotex for patent infringement within 45 days of receipt of notice of the ANDA. That patent infringement action stayed the approval of Apotex's ANDA for 30 months, until November 21, 2000, under section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)(5)(B)(iii)).

SmithKline was issued patent '132 in February 1999 and filed information on the patent with the Agency within the 30-day period described in section 505(c)(2) of the Act. In May 1999, SmithKline was issued patent '423 and again submitted patent information within 30 days. FDA listed the patents in the Orange Book as required under section 505(c)(2) of the Act.

Apotex submitted paragraph IV certifications for patents '132 and '423. SmithKline did not sue Apotex over the '132 patent, but did sue Apotex for infringement of the '423 patent on August 9, 1999. Because SmithKline sued Apotex for infringement of the '423 patent, FDA may not finally approve the Apotex ANDA until the patent litigation is resolved, or the 30 month period from the date SmithKline received notice of Apotex' certification to the '432 patent has elapsed.

II. Discussion

A. Listing of the '132 and '423 Patents

You claim the Act does not allow patents to be listed after NDA approval if patent information was already filed with the NDA before approval (Petition at 7). You conclude that because the '723 patent information was submitted before the Paxil NDA was approved, SmithKline could not file any additional patents after Paxil was approved in December 1992. You state that "[t]o interpret the statute otherwise thwarts the legislative objective of encouraging generic competition and provides an NDA holder with opportunities to manipulate the patent system and FDA's procedures for listing patents" (Petition at 8).

FDA's regulations implementing the patent listing provisions of the Act[2] require applicants to submit patent information for publication, even if that patent information is submitted after the NDA is approved, and regardless of whether patent information was also submitted at the time of filing or approval. Section 505(b)(1) of the Act requires the NDA applicant to file, and us to publish,

> the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture use, or sale of the drug.

Section 505(c)(2) of the Act states that

> If the patent information described in [section 505(b)(1)] could not be filed with the submission of an application under [section 505(b)] because the application was filed before the patent information was required under [section 505(b)(1)] or a patent was issued after the application was approved under such subsection, the holder of an

[2] Sections 505(b)(1) and 505(c)(2) of the Act.

> approved application shall file with the Secretary, the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under [section 505(b)(1)] because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after [September 24, 1984], and if the holder of an approved application could not file patent information under [section 505(b)(1)] because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

The language of this section is ambiguous and permits multiple interpretations. It is not clear whether the statute contemplates submission of information on a newly issued patent only when no patent at all was available for submission and listing at the time the application was filed or approved, or whether such information on newly issued patents may be filed after approval if the patent to which that information pertains was not available at the time of filing or approval of the application. Either interpretation is supported by the statutory language, and each has certain implications for the dynamics of the patent listing process. However, the Agency properly adopted the interpretation embodied in its patent listing regulations at 21 CFR 314.53(d)(3) through notice and comment rule-making. This regulation governs what patents may be listed and when such information must be submitted to FDA. [3]

You further request that if we do not delist the '132 and '423 patents, we should waive the certification requirements with respect to those patents. You refer to our regulation that exempts ANDA applicants from patent certification requirements for patents that were not timely filed under section 505(c)(2) of the Act.

That regulatory provision, 21 CFR 314.94(a)(12)(vi), however, does not govern cases in which patents were properly filed either before NDA approval or within 30 days of patent issuance. Our regulations instead make clear that patent certification is required by ANDA applicants for properly filed patents (section 314.94(a)(12)(i)). The '132 and '423 patents were filed within 30 days of patent issuance. Therefore, ANDAs referencing Paxil are required to file appropriate certifications with respect to those patents.

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[3] The Agency has been asked to reconsider its interpretation of the statutory provisions governing patent listing, patent certifications, and the 30-month stay under section 505(j)(5)(B)(iii) because of growing concerns that innovator companies are abusing the current interpretation and unreasonably delaying approval of generic drugs. A number of the comments on the proposed rule, *180-Day Generic Drug Exclusivity for Abbreviated New Drug Applications*, 64 Fed. Reg. 42873 (Aug. 6, 1999)(Docket No. 85N-0214), addressed these issues. The Agency is considering revisiting its interpretations in an additional rule-making.

B. FDA's Role in Patent Listing

You state that we have "the authority, expertise and obligation to ensure that listed patents actually claim the drug FDA approves in an NDA" (Petition at 18). You also assert that "[i]t is plain that FDA will be able to look at" SmithKline's patents and determine that the '132 and '423 patents do not claim paroxetine hydrochloride hemihydrate (Petition at 18). You conclude that we can determine that the patents were improperly listed and should delist them from the Orange Book. You further assert that we cannot rely on private litigation between ANDA applicants and NDA applicants to ensure that patents are properly listed (Petition at 17).

FDA has consistently viewed its role in the patent listing process as ministerial. The Agency does not independently assess whether a patent covers the approved drug product. FDA's limited role in patent listings is fully consistent with the statute and legislative history. The Act does not mandate the kind of critical review of patents you would have this Agency conduct. We are directed to publish patent information, not to analyze the patent submissions.[4] Our regulations address those responsibilities by setting forth our listing procedures and the process for responding to patent listing challenges. Our listing procedures include informing applicants about what patent information is to be submitted, who must submit the information, and when and where to submit the information.[5] We also describe the process for correcting patent information errors.[6] We require written notification of the grounds for a dispute as to the accuracy or relevance of patent information. Upon receipt of this notification, we request the NDA holder to confirm the correctness of the patent information.[7] We will only change the patent information in the Orange Book if that information is withdrawn or amended by the NDA holder.

Our role in evaluating patent listings is very limited. We do not have the resources or expertise to evaluate patent coverage issues for listed patents.[8] We specifically addressed this position in responses to comments on our proposed rule[9] regarding implementation of the patent and exclusivity provisions of the Hatch-Waxman amendments to the Act.[10]

The statutory scheme evidences clear Congressional intent to have the courts, not the Agency, decide issues of patent infringement and validity.[11] Our role is to publish patent information and thus advise interested parties of intellectual property protections that NDA sponsors claim apply to the innovator product. Publishing the information allows for ANDA and NDA applicants to avail themselves of the judicial system to determine the patent issues, as contemplated in the Hatch-Waxman amendments. Issues of patent validity and coverage can be extremely complex and may involve much more than what you describe as scientific evaluations of the patent claims

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[4] Sections 505(b)(1) and 505(c)(2) of the Act.
[5] 21 CFR 314.53(a), (b), (c), and (d).
[6] 21 CFR 314.53(f).
[7] Apotex did not follow this procedure.
[8] See 54 FR 28872 (July 10, 1989) at 28909-10 (proposed rule implementing Hatch-Waxman amendments to the Act).
[9] See 59 FR 50338 (October 3, 1994) at 50345.
[10] Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law No. 98-417, 98 Stat. 1585 (1984)).
[11] See section 505(j)(5)(B) of the Act; see also 59 FR at 50345, 50348.

(Petition at 15-16).[12] The statutory 30-month stay on ANDA approvals following initiation of patent litigation affords the opportunity for these potentially challenging issues to be resolved through the courts. An ANDA applicant sued as a result of its paragraph IV patent certification may certainly raise in that litigation the threshold issue of whether the patent was properly listed in the Orange Book. This would involve a determination of whether the contested patent covers the approved drug.[13]

D. Correctness of Patent Filings in this Case

You state in your comment to the petition that the declarations SmithKline submitted in support of the '132 and '423 patent listings do not comply with our regulations. You state that we should delist the patents because of the alleged deficiencies (Comment at 1, 5).

The listing of the '132 and '423 patents complies with the statute and with FDA regulations. The regulations governing submission of patent information require an applicant to submit any patent that covers "the drug or a method of using the drug that is the subject of a new drug application," including drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents.[14] The applicant must submit the patent number and expiration date, and what type of patent it is. If it is a formulation, composition, or method of use patent, the applicant must also submit a declaration as described in the regulations.[15] SmithKline complied with these requirements in submitting its patent information.

You claim that SmithKline's patent submission is deficient because it does not contain an adequate declaration. The declarations are sufficient to support the patent listings. They state that the '132 and '423 patents claim the approved drug product Paxil, paroxetine hydrochloride. However, it should be noted that declarations are not required for drug substance patents, such as the '132 and '423 patents. Such declarations are required only for formulation, composition, or method of use patents (section 314.53(c)(2)). Therefore, the declarations submitted by SmithKline were not deficient.

D. Scope of the '132 and '423 Patent Claims

You specifically assert that SmithKline improperly caused us to list the '132 and '423 patents because neither patent claims the drug that is the subject of the Paxil NDA. You state that SmithKline's NDA is for paroxetine hydrochloride hemihydrate, which is covered by the '723

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[12] It is worth noting that in this highly litigious environment, a decision by FDA that a patent does not cover an approved product and thus may not be listed, would doubtless lead to an entire round of complex and time-consuming litigation on the nature of the approved product, and the validity and scope of the patent, even before an applicant files an ANDA seeking approval of a generic form of the drug. This would not be an appropriate use of Agency resources.

[13] See, for example, *Zenith Laboratories, Inc. v. Abbot Laboratories*, Civ. No. 96-1661 (D.N.J. Aug. 7, 1996)(court concluded that an analysis of certain technical characteristics of the drug substance was necessary to determine whether it was the same active ingredient as the approved drug); *Ben Venue Laboratories, Inc.* v. *Novartis Pharmaceutical Corp*, 10 F. Supp. 2d 446 (D.N.J. 1998) (court concluded that a patent claiming the crystalline pentahydrate form of pamidronate was very likely properly listed although the approved drug product was an anhydrous form of pamidronate, not a pentahydrate form).

[14] 21 CFR 314.53.

[15] 21 CFR 314.53(c)(2).

patent filed before the application was approved. You point out that the '132 and '423 patents are for anhydrate, not hemihydrate, forms of paroxetine hydrochloride. You conclude that because the two patents claim different hydrous forms of paroxetine hydrochloride, they do not claim the listed drug, Paxil.[16]

Patents must be listed if they claim the drug substance, or active ingredient, of an approved drug product, or if they claim a drug substance that is the component of such a product.[17] SmithKline has submitted the '132 and '423 patents as covering the active ingredient of Paxil, listed in the Orange Book as paroxetine hydrochloride. Therefore, FDA has listed these patents in the Orange Book. FDA has made no independent assessment of whether patents '132 and '423 claim the approved drug product; it relies upon SmithKline's assertions on this point.[18]

III. Conclusion

For the reasons described above, we deny the requests in your petition and comment. We will not remove the '132 and '423 patents from the Orange Book. All ANDAs referencing Paxil, therefore, must submit appropriate certifications to those patents.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[16] Please note that for purposes of the same active ingredient requirement in 505(j), FDA considers anhydrous and hemihydrous forms of drug substances to be pharmaceutical equivalents and to contain the same active ingredient (Orange Book (20th Ed. 2000), at xv, vii). Paroxetine hydrochloride anhydrate and paroxetine hydrochloride hemihydrate are pharmaceutical equivalents and contain the same active ingredient, paroxetine hydrochloride. Apotex is seeking to have its ANDA for an anhydrous paroxitine hydrochloride approved as a pharmaceutical equivalent to Paxil, which contains the paroxitine hydrochloride hemihydrate.

[17] 21 CFR 314.53(b).

[18] FDA's position is fully consistent with *Pfizer* v. *FDA*, 753 F. Supp. 171 (D. Md. 1990). That case stands for the proposition that NDA holders may submit to FDA for listing in the Orange book only patents covering the approved drug product. *Pfizer* involved the question of the listing of patents for a drug in a dosage form other than the dosage form approved by FDA. The court agreed with the Agency's interpretation of the statute to permit listing of patents only on approved drug products. That requirement — that a patent submitted to FDA cover an approved drug product — is embodied in 314.53(b).